Core and Collaborative Research Project Descriptions (cont'd.)

(3) The program uses metastable peaks to determine parent-daughter relationships between ions and thus to distinguish molecular ions and their primary fragments.

Programming for the analysis of spectra has been completed. The program and results are described in a forthcoming article:

Smith, D.H., et al., "Applications of Artificial Intelligence for Chemical Inference:VIII: An Approach to the Computer Interpretation of the High Resolution Mass Spectra of Complex Molecules. Structure Elucidation of Estrogenic Steroids," Journal of American Chemical Society, in press.

Analysis of the mass spectra of pregnanes will be the next task for the computer program. Work is under way to collect the data from several pregnane samples and to allow the program to use a less well-defined theory for this class than for estrogens.

The artificial intelligence interests of the DENDRAL groups are reflected in work in program generality, partly described in reference (A), and in the program called meta-DENDRAL described in reference (C), which will infer mass spectrometry rules from collections of data. Parts of the meta-DENDRAL program have been written which codify observations about mass spectrometry, and work has started on the succeeding phase of the program which will generalize these observations into tentative rules.

A. Feigenbaum, E.A., Buchanan, B.G., and Lederberg, J. "On Generality and Problem Solving: A Case Study Using the DENDRAL Program", in Machine Intelligence 6, B. Meltzer and D. Michie (eds), Edinburgh University Press, 1971.

B. Buchanan, B.G., and Lederberg, J. "The Heuristic DENDRAL Program for Explaining Empirical Data", presented at the 1971 Congress of the International Federation of Information Processing Society (August, 1971) and published by North Holland Publishing Co.

C. Buchanan, B.G., Feigenbaum, E.A., and Lederberg, J. "Beyond Heuristic DENDRAL", presented at the International Joint Conference on Artificial Intelligence (September, 1971) and published in the Proceedings.

This system plans to incorporate a high degree of computer control. The goal of the instrumentation project will be to combine the analysis of the DENDRAL computer program with the data acquisition and control capability of the computer. It is planned to do a fast preliminary data acquisition, let the DENDRAL program determine what additional data and data mode is desirable, have the computer control the instrument mode and data scan, and return the pertinent data to the DENDRAL program. Further iterations of this cycle can be repeated as long as the sample persists.

A GLC (gas chromatograph) has been connected to one inlet of the mass spectrometer. The persistence of a given sample is determined by the duration of the GLC peak, a few seconds to half a minute. We have the type of mass spectrometer which usefully takes data in many modes: low, high, ultra-high, resolution and meta stables, high or low ionization potential, etc. It cannot

Core and Collaborative Research Project Descriptions (cont'd.)

acquire all this data in the time span allowed by a single GLC peak. Hence
it is desirable that the computer determine, during the limited sampling
time, the most useful mode of operation, and then implement this optimum mode.

Dispersed Computer for Instrumentation

During Fiscal 1972, support was given to the development of the "HIQ" remote
smart terminal. This was in cooperation with Professor Melvin Schwartz of the
Physics Department, with joint NASA support and Air Force support under con-
tract AF F 44620 67C 0070.

This cooperation did develop a unique Direct Memory Access unit for the PDP-11.
This portion of the project is concluded. The experience and concepts of
that joint effort are now integrated with the realization and future planning
of the instrumentation for the DENDRAL project.

This PDP-11 is now being used as a satellite computer to the IBM 360/50 in the
data acquisition from the mass spectrometers. As such it is used to prepro-
cess data streams from the mass spectrometers.

The general pattern for system development is to use the larger resources of
the ACME 360/50 to develop algorithms. Program techniques may be tried and
proved either on real data streams or on files of data from prior instrument
runs. After an algorithm has been thus proven, it can be encoded into the
less flexible local computer code.

This experience and experiments with this master satellite system are proving
invaluable to the economical and adequate selection of the next generation of
DENDRAL requirements. (Considerations for this next generation have ranged
from a re-dedication of the present hardware to an all new system with a new
master and satellite chains of small computers. No firm decision has yet
been made.)

In the Summary of Computer Resource Usage, DENDRAL usage is listed under the
following names and projects.

Bob Berns	LISP
Larry Hjelmeland	DENDRAL
Walter Reynolds	DENDRAL
	DREAMS
Tom Rindfleisch	DENDRAL
Robert Ross	CHEM
	DENDRAL
Mark Stefik	DENDRAL
Robert Stillman	DENDRAL
	DREAMS

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the DENDRAL research project.

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Core and Collaborative Research Project Descriptions (cont'd.)

Investigator: Stan Cohen
Dept. of Medicine, Div. of Clinical
      Pharmacology
Project Began October 1969

Project: SNCOHEN. DRUGALRT
Non-Realtime
Chargeable Use Began December 1971

The project involves the establishment of a computer-based program aimed at preventing undesirable drug interactions and reducing drug toxicity at the Stanford University Medical Center. A data bank dealing with drug interactions of clinical significance will be compiled utilizing already available information present in the pharmacological literature. When prescriptions are filled by the Stanford pharmacists, the pharmacists will type the name of the drug and the dosage regimen into a terminal located in the Hospital pharmacy. When a new drug added to a patient's regimen interacts with any one of the several drugs the patient may already be receiving, the computer will print out an appropriate drug interaction alert accompanied by a literature reference, which will then be sent to the nursing unit by the pharmacist-- together with the drug. Prior to administering a drug accompanied by such an "alert", the nurse will contact the physician in charge, who will retain the prerogative of deciding whether or not the drug should be administered. This program will provide considerable teaching benefits to students and house staff, in addition to providing benefits of major importance to patient care. In addition, it will be possible to assess the impact of providing physicians with drug interaction information, and also to learn in a prospective way about the clinical consequences of drug interactions.

Initial operation of the system began in September 1971. Since it was anticipated that production of drug interaction warnings would influence the prescription writing habits of physicians, it was desirable to obtain baseline information on drug use, duration of hospitalization and other parameters in various diseases at Stanford University prior to generation of interaction reports. Moreover, in the initial stages of the project, it was desirable to evaluate the ability of the pharmacist to rapidly enter the additional prescription information the system requires without disrupting normal pharmacy routines, and to determine whether an on-line interactive video display unit and label printing program would function effectively in a busy in-patient hospital pharmacy. At the present time, accumulation of baseline information on drug utilization is continuing, and routine interaction reports are not yet being issued.

In the future, it is anticipated that the program will be extended to other hospitals, and a modified version is currently under development that will be usable in community out-patient pharmacies. It is also expected that the program will interface with the laboratory test program which has recently been developed by Dr. Howard Sussman. Once this interface has been accomplished, it will be possible to utilize prescription information in evaluating laboratory test results. Thus, laboratory evidence of inadequate renal function might serve to alert the physician not to administer usual doses of a drug that is excreted entirely by the kidney. Conversely, the artifactual effects of certain drugs on laboratory test results can be detected and appropriate warnings provided in the clinical laboratory.

COLLABORATIVE RESEARCH PROJECTS

Investigator: Christos Constantinou   Project: C_CONSTA. UROL
Dept. of Surgery, Div. of Urology   Realtime
Project Began November 1969

Studies are being done to improve the clinical appraisal, follow-up and management of patients with neurogenic bladder dysfunction secondary to spinal cord injury or disease. In particular, we are trying to determine the feasibility of utilizing computer-based techniques of information data storage, processing and retrieval in this patient population.

Of particular interest is the mechanism of initiation of peristaltic waves and the quantitative description of the process through which continuous urine flow at the kidney is transformed to discrete peristaltic waves. The significance of this transformation lies in the rhythmic properties of the output sequence of peristaltic waves, and the stroke volume of each wave. These two variables alone provide the most convenient measures for ureteral function evaluation. A hypothetical model has been developed to simulate the generation of peristaltic wave trains with the objective of developing a manageable description of their temporal sequence. Spike train analysis traditionally employed in statistics has been used for this purpose. It is expected that in the course of development of the mathematical model, a better understanding of what is responsible for the observed process will result. As a consequence, it will be possible to make inference as to whether the ureteral system is driven by a neuronal pacemaker or is myogenic.

ACME is being used for real-time data acquisition and feedback, and for analysis. Analog data collected from anesthetized animals in surgery is transmitted via the interface box to the 1800 and 2741 output received in the operating room during the experiment.

Investigator: Eugene Dong   Project: E_DONG. LAB
Dept. of Surgery, Div. of Cardiovascular   Realtime
   Surgery
Project Began November 1970

The primary purpose of the project was to study the principles of mammalian heart rate control, with particular emphasis on the sino-atrial node--the controlled pacemaker which governs heart rate. Since understanding the pacemaker requires a mathematical description of its behavior, a concomitant objective was to quantify observed heart rate data.

The contributions of this research should be helpful in interpreting the functional status of the central nervous system from observed heart rate data. They are basic to understanding respiratory sinus arrhythmia and ventriculophasic arrhythmia and are also pertinent to establishing control criteria for artificial heart assist and replacement devices.

<u>Collaborative Research Project Descriptions (cont'd.)</u>

The control of mammalian heart rate was studied by first eliminating normal central nervous control to the heart and then artificially evoking impulses in the nerves leading to the heart. The work was restricted to an analysis of the effect that vagal nerve impulses have on resulting decreases in heart rate.

In these experiments, the heart was placed in an autonomous state by severing both cervical vagal nerves and administering the beta adrenergic blocking agent propranolol. Heart rate responses were then elicited in 14 anesthetized dogs by electrical stimulation of the cut end of the right vagal nerve. Each stimulation was varied in intensity and in time relative to the heart cycle.

Computer controlled stimulations yielded reproducible temporal sequences of heart periods for the two testing schedules employed. For one schedule, the system was impulsively perturbed by one stimulation. For the other, a train of stimulations reproducibly forced the system to a second state, where it was either perturbed further by one stimulation or permitted to relax to the autonomous state. The new measurements obtained demonstrated that existing mathematical models of heart rate control functions are incomplete.

A model consisting of coupled, first-order, nonlinear differential equations was formulated to predict the heart period first lengthened by one stimulation; the measured periods ranged to three times the autonomous period. For

ɔn the intensity and relative timing of
the hypotheses that

:oncentration of the neurotransmitter
ɔes in negligible time and then exponen-
msec half-life time--one-twentieth the
: to relax to the autonomous rate; and
ɔ, 175 msec period prior to the end of
ɔ is continuously controlled.

ɪr difference equation, describes the
ɔen the input and output pulse trains of
ɪ oscillators. Necessary and sufficient
ʒiven for synchronization of input and
ɪental frequency. The derived analyti-
ɔ to the analysis of heart rate data ob-
ɔuency, vagal nerve stimulations.

are as follows:

e above the autonomous rate which are
gal nerve stimulation are reported;
e of the transient relaxation of heart
following the cessation of stimulations;
  smallest observable time for a stimula-
d the dependence of this time on the
h;
nsiveness to a stimulation is shown to

ɪaɔeu ɔhe dependence ot heart period ɔ
the stimulation. The model supports ɪ

(1) after one stimulation, the ɔ
     at the heart's pacemaker riɛ
     tially decreases with a 400
     total time for the pacemakeɪ
(2) except for an uncontrollablɛ
     each heart cycle, heart ratɛ

A second model, a first-order nonlineɛ
temporal sequence of time delays betwɛ
a class of injection-locked relaxatioɪ
conditions on the nonlinear term are ɡ
output when they are of similar fundaɪ
cal results are shown to be applicablɛ
served under repetitive, constant freq

Other extensions to previous research

(1) large increases in heart rat
     paradoxically produced by va
(2) quantitative analysis is mad
     rate to the autonomous rate
(3) measurements are made of the
     tion to affect heart rate an
     unaffected heart cycle lengt
(4) the decrease in system respo:

Collaborative Research Project Descriptions (cont'd.)

        be dependent upon the short term past history of stimulations;

(5) measurement is made of the recovery of responsiveness that occurs following the cessation of stimulations; and

(6) the time required for complete recovery of responsiveness is shown to exceed the total time required for heart rate to return to the autonomous rate.

During the latter part of this fiscal year, a part-time ACME programmer has developed additional graphics tools for this project. Scatter plotting of experimental parameters, and historical plotting of treatments are included.

Investigator: Eugene Dong
Dept. of Surgery, Div. of Cardiovascular
  Surgery
Project Began July 1970

Project: E_DONG. PATIENT
                      Realtime

ACME has been used to enter and store data from over 1800 cardiac surgery patients. Data includes age, diagnosis, admission data, operation date, discharge date, and operation description.

Using this data base, weekly and monthly operating schedules are generated. Survival tables are produced for the transplant patients, and some correlation work is done with the entire data base. Tables of patient data (ordered by hospital number and last name) are also generated.

Investigator: Alan Duffield
Dept. of Genetics
Project Began December 1968

Project: VABACON. GAME
                      Realtime

In this "on-line" application, the decision-making capabilities of the computer are coupled with those of an operator to direct the operation of a Finnigan 1015 quadrupole mass spectrometer.

The computer is used to actively direct the operation of the mass spectrometer by controlling the mass filtering system of the instrument. It is used to recognize and control the voltage changes which define mass peaks and enable the rapid collection and presentation of data.

The computer traces out peak shapes of the known masses in a reference gas allowing the operator to determine correct mass positions, and to enter any shifts in calibration into the computer register for compensation automatically.

While taking data, the information may be displayed on an oscilloscope or recorded on magnetic tape. Once data is acquired, the structural identification of organic compounds is made from orthogonal coordinate or spiral base plots

Collaborative Research Project Descriptions (cont'd.)

of mass spectra made by computer direction of a CALCOMP plotter. The system
is also used to analyze Gas Liquid Chromatograph effluent, permitting the
structural identification of mixtures of organic compounds. This last appli-
cation has important uses in the analysis of organic compounds from biologi-
cal sources.

Investigator: James Fries   Project: J_FRIES. DATABANK
Dept. of Medicine, Div. of Immunology   Non-Realtime
Project Began July 1969

This project involves a primary clinical information retrieval system which
interrogates computer-stored accumulated patient experience and obtains data
for direct answers to clinical and research questions.

The present non-indexed disorganized methods of maintaining medical records
represent an obstacle to good patient care, a hindrance to medical education
and a limit on the quality of medical research. This project attempts to re-
move these obstacles by implementation of a structured method of data col-
lection and entry of the structured data into a computer databank. Search
programs operating on the databank provide prompt, accurate recall of past
experience and correlations with new developments. The databank is contri-
buted to and used by physicians in private practice as well as those of the
university center. The structure of the computer file is designed to maxi-
mize "search" efficiency and a library of output program allows the immediate
answering of many millions of possible clinical questions by retrieval, tabu-
lation, and statistical manipulation of primary patient data.

A systematic method of recording serial clinical and laboratory information
has been developed and clinically tested. The method has two important fea-
tures:

    (1) As a "time-oriented record" it displays changes in parameters with
         respect to time so that the entire past course of the patient can
         be quickly analyzed by the physician.
    (2) It replaces rather than adds to present records.

These features improve physician acceptance as well as scientific validity.
The chart reduces redundancy and decreases total "paper work" by the physi-
cian.

Factual clinical information is displayed in a two-dimensional time-oriented
format, listing parameters on the vertical axis and time on the horizontal.
Time is represented by successive "patient-visits" in which each encounter
of a patient and a physician is considered a data-gathering point and forms
one column of the chart. Laboratory data and the therapeutic program are
similarly entered on the record.

If the course of a patient may be displayed in two dimensions, then a com-
puter databank may be considered a three-dimensional array of data. Data

Collaborative Research Project Descriptions (cont'd.)
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thus arranged may be located directly by the use of three coordinates, and
search procedures may be operated on the parameter axis, the time axis, or
the patient axis with equal ease. A search may be addressed to various para-
meters of one patient, to changes with time, or to findings in groups of
patients. Interrelationships of parameters are easily investigated, and
questions involving the time axis, such as prognostic importance of varia-
bles or response to therapy, may be answered.

In our system, information is entered into an IBM 360/50 digital computer
by use of a typewriter terminal. Ten new patients, fifty patient visits,
and about 20,000 pieces of data are entered each week. Three hundred and
fifty-two entries are made for each patient visit. Daily search procedures
acting on the databank provide research data, support individual clinical
decisions, and develop experience-based data for clinical teaching.

Our computer is frequently consulted instead of a traditional medical-lib-
rary-based review of the literature, as the databank often contains a series
which is larger, more recent, more accurate, and more directly applicable to
our patient population. Moreover, if expenditure of physician time is con-
sidered, consultation with the computer is generally less expensive than
utilization of the library.

Computer storage of detailed clinical information has been feasible, desir-
able, and useful in our clinic, and by extension, should have wide applica-
tion within medicine. The clinical databank is a powerful tool which can
serve as the central focus for teaching, research, and patient-care activi-
ties. By development of improved methods of handling and analyzing patient
data the clinician and the clinical researcher may be able to effectively
utilize the increasing flow of biological information from our laboratories.
Design of improved clinical charts, methods of computer file organization,
formats which output data should assume, and potential interchange of
clinical information between institutions are crucial medical questions,
and evolving answers to these questions will play an important part in
determining the quality of future health delivery systems.

Investigator: Jerome Gold   Project: J_GOLD. SWALLOW
Dept. of Radiology, Div. of Diagnostic   Realtime
   Radiology
Project Began October 1969

This project involves the study of esophageal blood flow.

One study compared the esophageal blood flow of normal subjects and subjects
affected with a connective tissue disease (CTD). Such diseases are character-
ized by esophageal motility abnormalities. The hypothesis was that these ab-
normalities were related to impaired blood flow. The blood flow was indirect-
ly assessed by measuring the time for intraluminal esophageal temperature to
rise to normal following ingestion of 5 ml. swallows of 0.5° C. ice water.
With the subject sitting, 2 small thermistors were inserted into the esopha-

Collaborative Research Project Descriptions (cont'd.)

gus, one located in the distal 1/3 and the other in the proximal 1/3 near the junctional zone of smooth and striated muscle. Thermistor rewarming curves were recorded and the amplified signals collected by ACME through the 1800 for storage and analysis. Thermistor curves were analyzed (deg/sec) for several portions of the rewarming time. A significant difference existed between the slopes of the first half rewarming in CTD patients and normals in the lower esophagus. Although of lesser magnitude, a significant difference also existed between the slopes of the first half rewarming in the upper esophagus. Preliminary evaluation suggests that the time for first half re-warming may also be significantly different between the two groups. These data provide additional support for the hypothesis that esophageal blood flow is decreased in some CTD and may be related to their manifest motor dysfunction.

A second study, utilizing laboratory animals, measured esophageal blood flow with injections of radioactive material. A catheter-type semi-conductor beta radiation detector system (catelix) was used. A detector was passed into the distal esophagus. Two millicuries of ^{86}Rb were injected intravenously, and ACME made continuous recordings of the Catelix counts per unit time over a ten-minute period. After ten minutes, another 2 mCi of ^{86}Rb were injected and counts again recorded. After serial determination, a final 2 mCi of ^{86}Rb were injected and the animal sacrificed 60 seconds later. The esophagus was removed. Counts were then recorded at different levels in the esophagus and correlated with the amount of ^{86}Rb per gram as determined by counting the tissue in a well-type scintillation counter. The data will be subjected to statistical analysis to evaluate the linearity of count rate with dose of administered isotope. The area under the curve generated by changing count rate after the isotope is administered may be used to calculate cardiac output.

By substituting another isotope and different dosages, serial determinations of esophageal blood flow are feasible in humans.

Investigator: Donald Harrison   Project: DCHARRIS. CATH_LAB
Dept. of Medicine, Div. of Cardiology   Realtime
Project Began 1968

Fourier analysis is being performed on left ventricular pressure curves. Their component points are stored for frequency spectrum quantitation. This study is done to determine the frequency response which the equipment must have in order to represent the data accurately. The results are applied to hemodynamic studies in both patients and experimental animals.

ACME is used for data handling for cardiology research on dogs. Normal dogs and dogs which have undergone various surgical procedures are involved in the study. Numerous hemodynamic values collected under a variety of experimental conditions are filed for each dog. These files provide a convenient source of reference and comparison for a number of cardiology researchers.

Collaborative Research Project Descriptions (cont'd.)

Investigator: Leslie Kadis   Project: L_KADIS. VISAEP
Dept. of Anesthesia   Realtime
Project Began July 1971

The purpose of this project is to develop a model for experimental pain that
will be clinically applicable. The model, based on the gate control theory
of pain proposed by Melzack and Wall, will be tested in man and in animals.

Sensory information from painful stimuli travels from peripheral receptors
to synapse with second order neurons ("T" cells) in the substantia gelatinosa
in the spinal cord over both large, fast conducting fibers, and small, slow
conducting fibers. Melzack and Wall proposed that transmission to the T cell
in the spinal cord depends on the balance between large and small fiber acti-
vity. For example, when large fiber activity predominates, the threshold for
excitability of the T cell is raised, or, in other words, the gate is closed.
Transmission of information about painful stimuli is then impaired. We will
study the role of disorganization of sensory information (change in the bal-
ance between large and small fiber activity) on transmission of neural im-
pulses in the spinal cord in cats. We also will assess the modification of
spinal cord activity by narcotics.

Another aspect of the Melzack and Wall hypothesis is that there is a separate
pathway for rapid transmission of sensory information directly to higher cen-
ters with feedback to the "Gate" to change the threshold for excitability of
the T cell. The averaged evoked cortical response (AER) to somesthetic stimu-
lation reflects both transmission at the spinal cord level and central pro-
cessing, and it is our hypothesis that individual responsivity to painful
stimuli can be predicted from the pattern of response of AER to graded
intensity stimuli. We plan to develop quantitative methods to test this
hypothesis using experimental pain in man.

We also plan to evaluate psychophysiologic aspects of experimental pain in
man, as well, and relate these to the pattern of response of the AER. We
know, for example, that individuals whose perceptual style is such that they
require perceptual clues from the external world, or who, in their interper-
sonal relationships are extroverts, or who have little anxiety, are most
tolerant of pain. The project will assess some aspects of personality (the
introversion - extroversion parameter) as well as cognitive and affective
variables and relate these to patterns of response of AER to graded intensity
stimuli.

Finally, the project will utilize the methods developed above and assess the
relationship between clinical and experimental pain in patients who are suf-
fering from cancer and who have metastases to bone. In this homogenous group
of patients we will correlate patterns of AER with clinical pain, response
to drugs, and methods of coping with illness to assess the relative importance
of these variables.

Collaborative Research Project Descriptions (cont'd.)

Investigators: Larry William and   Project: S_ROSENB. MEDONCOL
  Saul Rosenberg   Non-Realtime
Dept. of Medicine, Div. of Oncology
Project Began 1972

The Division of Oncology has recently begun to experience an increasing need
for a versatile medical record data processing system to serve both patient
care and research requirements. To achieve these goals we are currently
attempting to modify a computer-based time-oriented medical record system
developed by the Division of Immunology.

Specifically, we are using a versatile input program to store approximately
450 different patient care parameters for each clinic visit. Thus, we are
currently inputting most of the hard data from the clinical charts of our
patients. Once a suitable data base has been established, we hope to be
able to obtain a variety of outputs. For example, we hope to nimbly re-
trieve, compare and display actuarial survival curves of patients treated
with competing therapies; search for laboratory tests which are of prog-
nostic significance; find patient subsets with uniquely good or bad respon-
ses to treatment, etc.

Initially we are exploring the advantages of this record keeping system on
the patients in the medical oncology clinic. If it proves feasible, we hope
to expand and generalize the programs so devised to apply to other problems
in oncology and general medicine.

A new time-oriented medical chart is an essential and unique feature of our
current system. Information is recorded in an efficient, basically flow-
sheet mode in the most objective fashion possible. Then this material is
input via the typewriter terminal into the 360/50 computer. The chart serves
as a hard copy of the patients' record and satisfies all medical-legal re-
quirements.

Investigator: Howard Sussman   Projects: H_SUSSMA. LABSYSO
Dept: Stanford Univ. Hosp.   H_SUSSMA. LAB_PAT
  Clinical Lab Pathology   H_SUSSMA. c1050937
Project Began November 1969   Realtime and Non-Realtime

Over time, the work load of the Clinical Laboratory has steadily increased.
At present, in the Chemistry and Hematology areas of the Clinical Laboratory,
over 2000 tests per day are performed on approximately 400 specimens. The
increased work load has put such a strain on the manual system that serious
problems have developed in specimen handling, and the gathering and dissem-
ination of information.

A Clinical Laboratory Information System has been developed at Stanford Hos-
pital using the ACME system. Mark-sensed card input to the patient data

Collaborative Research Project Descriptions (cont'd.)

Investigator: Gerald Reaven
Dept. of Medicine, Div. of Metabolic
  Diseases and Endocrinology
Project Began January 1969

Projects: G_REAVEN. PAT_DATA
            G_REAVEN. DISPLAY
                 Non-Realtime

We are involved in studies of the relationship of risk factors such as choles-
terol, etc., to coronary heart disease in the community. This study involves
the use of ACME in three major ways:

(1) We utilize ACME's data storage and retrieval capabilities. The
     data collected consists of variables describing the demographic,
     medical and behavioral characteristics of the subjects in the
     study. Our first major study was just recently published and
     the ACME facility was used almost exclusively.

(2) We use the library of statistical programs in conjunction with the
     retrieval capabilities of ACME to analyze community data.

(3) We have used the graphic capabilities of ACME to develop an inter-
     active graphic pattern recognition procedure which describes the
     underlying distribution of the data obtained from the community.
     It also is an exploratory mechanism to determine if the distribu-
     tion may consist of sub-component populations. We are also capa-
     ble of estimating in another graphic subroutine the parameters of
     the resulting component populations if they are bivariate Gaussian.

A second major research activity consists of developing mathematical, phy-
siological and computer models describing the production, distribution and
removal of certain metabolites important in the study of diabetes mellitus
and atherosclerosis. In the past, we have developed and updated a model
describing the distribution and degradation of insulin in man and dog. We
have, in conjunction, developed graphic computer techniques to aid us in this
model building. The distribution and uptake of glucose in man has also been
considered and a paper is forthcoming describing a comparative study of the
dynamics of the glucose and insulin systems. A prior paper described the
efficiency of glucose uptake in normal and diabetic man and has utilized both
the graphic and statistical capabilities of ACME.

We are now developing models that describe the mechanisms of insulin pro-
duction in man and dog and the effect of glucose on this secretory system.

Another important aspect of our work concerns inpatient metabolic problems,
and we are at present involved in establishing a data file on ACME for two
specialty clinics. We hope to use ACME's storage, retrieval and statistical
capabilities to analyze this data in order to explain various mechanisms that
may be responsible for some of the etiology of maturity onset diabetes and
atherosclerosis.

We are also involved in the development of a nationwide clinical trial to test
the "lipid hypothesis" and are utilizing ACME to develop statistical models
which can explain the interrelationship of the parameters associated with
this clinical trial.

Collaborative Research Project Descriptions (cont'd.)

files is provided using a mark-sensed card reader tied into the IBM 1800 at ACME. The system prints worklists for the technicians and monitors the status of the tests which have been ordered. At the end of each day, the patient results are printed in a form suitable for chart copies or lab files.

A multiple analyzer, the SMA 12/60, has been interfaced to the IBM 1800 to provide an efficient way of inputting test results to the patient files. In the future, more instruments will be interfaced.

At present, the Clinical Laboratory Information System is in pilot production mode at the Hoover Pavilion, a small hospital adjacent to Stanford. Using the lessons learned from operations there, the system will eventually come into production for the whole of Stanford Hospital.

Investigator: George Swanson   Project: G_SWANSO. THESIS
Dept. of Anesthesia   Realtime
Project Began September 1969

The respiratory laboratory in the Department of Anesthesia has been involved in the investigation of dynamic experimental techniques for the study of the human respiratory control system. Our goal has been to develop non-invasive experimental techniques in which we can assess human respiratory drug effects in terms of specific physiologic mechanisms which contribute to respiratory control.

The classical steady state and rebreathing experimental methods are restricted to assessing drugs in terms of an integrated respiratory effect. Our experimental approach uses the temporal aspects of a ventilatory response to an end-tidal CO_2-O_2 stimulus to observe and isolate the contribution of specific mechanisms such as the central chemoreceptor, cerebral blood flow, carotid body and lung to brain circulation time.

For the past year we have been involved in a theoretical study of dynamic experimental design. We have developed a dynamic end-tidal forcing technique. The basic idea is that the end-tidal time histories of CO_2 and O_2 can be selected for model discrimination and for minimizing the uncertainty in a model parameter estimate.

The design of experiments depends upon computer simulation of alternative models. We have implemented a descriptive computer simulation of the respiratory system. The simulation is general enough to encompass alternative configurations of interest. We have also validated via computer simulation, a theoretical method of selecting the end-tidal CO_2-O_2 forcing function for minimizing the variance of estimated model parameter.

The experimental design is enhanced through man-computer interaction. This concept was explored on ACME using the Tectronix display scope. Alternative forcing functions were generated and evaluated.

SERVICE PROJECTS

Investigator: Malcolm Bagshaw   Project: M_BAGSHA. SUMMARY
Dept. of Radiology, Div. Radia-   Non-Realtime
  tion Therapy
Project Began December 1968

The project contains datasets for four general purposes, listed below in the
order of disk storage space occupied.

The purpose of the first two groups of files and programs is to allow the
medical staff to conduct research on various forms of cancer and make com-
parisons of various methods of treatment.

    (1)   Files of records of general data on all patients of the Radiotherapy
        Division are kept from about 1968 to the present with the necessary
        programs for input and retrieval of the data. The retrieval pro-
        grams are designed to allow the radiologist himself to select pa-
        tients based on any desired criterion, print out desired informa-
        tion about each, or create a subset of these patients for further
        analysis.

    (2)   Another set of files contains records of detailed data on all pa-
        tients with Hodgkin's Disease, along with the necessary programs
        for input and retrieval of the data. The retrieval programs will
        choose records of patients selected on any combination of desired
        criteria, print out desired information about each, and perform
        survival or remission analysis on the selected group.

    (3)   Mathematical programs have been developed for use by the radiologic
        physicists for calculations concerning beam characteristics, depth
        dose tables, analysis of curves, etc.

    (4)   Statistical programs are available to obtain Berkson-Gage or Kaplan-
        Meier survival tables from data input by the user.

Investigator: Walter Bodmer   Project: W_BODMER. POPGEN
Dept. of Genetics   Non-Realtime
Project Began December 1968

Since the original discovery of sera with isoantibodies directed against
human white cell antigens, the use of statistical techniques has played a
major role in the discovery and analysis of human white cell antigen systems.
Stanford's Department of Genetics has long been involved with the development
of statistical analysis. The computer has always been one of our most basic
tools.

White cell antigens are now known to constitute the major human histocompa-
tability system, called HL-A. They form the basis for tissue typing for
clinical transplantation. Recent data has also shown significant correlation
between the HL-A system and certain diseases, notably Hodgkins disease. It
is also related to certain other cancers and to autoimmune diseases.

Service Project Descriptions (cont'd.)

The analysis of 2 x 2 associations between serum reactions for the definition of antigens in the HL-A system was pioneered in 1962 by Van Rood and has been further developed and extended by ourselves and others. It has been the basis for the definition of most of the presently known antigens of the HL-A system. The main principle involved is the recognition of groups of associated sera which share antibodies and can therefore be used to define the corresponding antigen. In addition, the analysis of association between antigens in populations has proved an important adjunct to understanding the genetic control of the HL-A antigens.

The improvement of serological techniques for the detection of white cell antigens has greatly helped in their definition. However, in order to have a basis for the original identification of new antigens and characterizations of sera, we find that it is still necessary to use the same statistical procedures which were originally essential for the definition of the antigens. Over the years, considerable effort has been invested in developing a library of programs for the analysis of serological data. This set of programs deals with all aspects of our work:

(1) input and organization of data
(2) characterization of sera
(3) assignment of antigen phenotypes
(4) calculation of population frequencies with respect to complex combinations of phenotypes
(5) fitting of complex genetic models to the phenotypic frequencies.

There is no doubt that the availability of the time-sharing system has greatly increased our ability to handle and analyze the large bodies of data involved in our research. Programs are designed for use by people who have no detailed programming knowledge. They include appropriate prompts for every stage of data input. During input, the data is monitored in various ways to verify that the input corresponds to expectations. Then the data is put into a standard format for subsequent ease of analysis. The computer is used at every stage of data analysis and interpretation. Examples are: the selection of subjects of a given phenotype to use for absorption, and the assignment of antigen phenogypes based on complex patterns of reaction to defined sets of sera. We have also developed programs for displaying population data on complex patterns of phenotypes and for the analysis of family data.

Investigator: Edward Bunnenberg
Dept. of Chemistry
Project Began December 1970

Project: E_BUNNEN. CHEM
　　　　　　　　　　Realtime

The main goal of this project is to achieve an effective interactive computer-assisted operation of a highly specialized type of spectrophotometer—a magnetic circular dichrometer. The utilization of organic chemical and especially biochemical applications of magnetic circular dichroism will allow the following:

(1) an increase in the operational sensitivity of the instrument

Service Project Descriptions (cont'd.)

        through the application of digital averaging and smoothing tech-
        niques. This is especially important for this instrument because
        of its inherent single-beam operation;

(2)   the measurement of compounds having relatively strong signals much
        more rapidly;

(3)   the extraction of quantitatively meaningful spectroscopic para-
        meters from the magnetic circular dichroism spectra. This is of
        crucial importance for much of the work and requires the implemen-
        tation of generalized curve deconvolution and fitting programs.

The first objective was demonstrated in the use of the MCD instrument with
on-line computer connection to analyze lunar soil extracts for metallopor-
phyrins.

Preliminary experiments indicate that the time required to scan through the
MCD spectrum of a routine sample, i.e., one in which the signals are rela-
tively strong, can be materially decreased through on-line computer operation
of the MCD instrument.

Significant progress has been made in connection with the third objective,
the extraction of quantitatively meaningful spectroscopic parameters from MCD
spectra, although fund limitations have necessitated this accomplishment by
off-line (curve tracer) rather than on-line computer assisted operation.

Investigator: Howard Cann   Project: H_CANN. GUAT
Dept. of Pediatrics   Non-Realtime
Project Began December 1968

This project is an investigation of factors which affect frequencies of genes
controlling various human heritable characters. The extent to which selec-
tion, genetic drift, and migration affect frequencies of certain human genes
is being assessed and specific selective factors are being sought. Environ-
mental, cultural, and historical conditions favorable for this type of study
have been found in settlements of Mayan Indian descendants in the Lake
Atitlan Basin of southwest Guatemala. The local microgeography and mating
patterns appear to enforce a high degree of genetic isolation for each of a
number of Indian towns and villages ringing Lake Atitlan. These high mortal-
ity populations provide the opportunity to study selection on human genetic
polymorphisms.

The ACME system stores demographic, clinical and socioeconomic data collected
from large samples of inhabitants of each of eight isolated Indian villages.
A master file for each village has been developed to link laboratory, demo-
graphic, and anthropological information on each individual. An indexing
system allows quick retrieval of each bit of data collected on a given indi-
vidual, as well as a means of linking him into a family unit, thereby retriev-
ing similar data from other members of his nuclear family. Using the various
data collected for and generated by this project, the ACME computer is now
being employed for the final analyses which will include maximum likelihood

<u>Service Project Descriptions (cont'd.)</u>

estimation of gene frequencies, analysis of variation in gene frequency dis-
tributions, estimation of coefficient of kinship from pedigrees, segregation
analysis of polymorphisms, comparison of fertility and mortality by genotypes
and association of clinical, epidemiologic and socioeconomic variables with
genotypes.

This project will also contribute information on the genetic taxonomy of the
American Indian. Families of large size, characteristic of the study popula-
tion, will afford excellent opportunities for medical genetic investigation
of inherited diseases encountered in our field activities and for studies of
genetic linkage.

Investigator: Luca Cavalli-Sforza   Projects: L_CAVALL. PAVIA
Dept. of Genetics   L_CAVALL. JUDY
Project Began March 1971   L_CAVALL. KEN
                                               L_CAVALL. LAURA
                                                L_CAVALL. MARK
                                                  Non-Realtime

<u>The Evolutionary Rate in Man</u>

Models have been developed for the reconstruction of phylogenetic trees.
These trees are developed to indicate not only relationships between and
among populations, but also to indicate the amount of time elapsed since the
separation of populations. Simulation is used (particularly in the determi-
nation of the amount of expected error in phylogenetic tree reconstruction).
Computer analysis is necessary in the construction and analysis of migration
matrices, genetic distance matrices, and gene frequency data.

<u>Changes in Man's Genetic Composition Brought About By the Spread of The Neo-
    lithic</u>

The Neolithic revolution has undoubtedly brought about some changes in the
genetic composition of man. The rate of spread and mode of spread have been
analyzed. Geographic maps with isochrones of the spread were drawn by the
computer, fitting the radiocarbon data to a surface. Analysis of the rela-
tion between radiocarbon time with the more accurate tree time is now being
carried out with polynomial fitting and search for periodicities. The
genetic effects will now be studied using the gene frequencies of various
polymorphisms, anthropometric measures, etc. In addition, simulations have
been set up to test the validity of the methods of analysis used.

<u>Patterns of Inheritance in Behavioral Traits Such as Schizophrenia</u>

Models have been developed, mainly using computer simulations, to throw light
on the possible modes of inheritance of such traits as schizophrenia. It is
hoped that such factors as penetrance, polygenic or single gene inheritance
can be brought into their proper relative perspectives.

Service Project Descriptions (cont'd.)

The Analysis of Record Linkage Data and Pedigree Information Based on Material Available from Parish Books, Census Data, Etc.

There is an on-going program of analysis of data, particularly from the Parma Valley of Italy. This data is obtained from parish books and from municipal records, as well as from Italian censuses. Such information as degree of inbreeding in the population, amount of migration, changes in life expectancy, family size, isonymy, etc. will be obtained from this study.

Investigator: Avram Goldstein   Project: A_GOLDST. OFFSTUFF
Dept. of Pharmacology   Non-Realtime
Project Began August 1970

The computer is used for filing and analyzing data from a clinical study on the use of methadone in the treatment of heroin addiction. The study is designed to answer questions about the efficacy of methadone in stopping heroin use and rehabilitating heroin addicts, to determine if there is an optimal dosage stabilization level for most patients, and to discover just what that dosage level is.

The subjects of this study are patients of the Santa Clara County Methadone Program and of several "sister" programs in this region. Data from several hundred patients is collected, in order to obtain a statistically valid sample, and the subjects are monitored in several ways:

(1) Urine samples are obtained on a random basis with a basic frequency of once in five days from each person. These samples are tested for the presence of morphine (heroin) and other drugs (barbiturates and amphetamines), and thus provide concrete evidence of the patient's progress or lack of progress, as measured by his continued use of heroin. ACME is used to file and analyze the results of the urine test, and also to generate the lists of random numbers which determine which patients give urine samples on which days, maintaining the desired frequency.

(2) Progress questionnaires (30 items, multiple choice) are administered to each patient at the time of admission to the methadone program and at regular intervals thereafter. These questionnaires provide data on physical symptoms while on methadone, current use of heroin, criminal activities, and occupation. This information is stored and analyzed statistically by ACME to discover correlations between success on the program and other characteristics, such as current dosage, age, sex, holding a job, etc.

(3) Symptom questionnaires are various short questionnaires (4-11 items) which deal primarily with physical symptoms and which are used to measure the patients' comfort on a particular dosage level or schedule. These questionnaires are administered more often than the progress questionnaire, usually weekly or daily, and have provided data for studies on determining the ideal dosage stabilization level, and on comparing once-daily and twice-daily administra-

Service Project Descriptions (cont'd.)

tion of methadone. This type of questionnaire will also be used in an upcoming study comparing the action of methadone and long-acting methadone (levorotatory-α-acetylmethadol, abbreviated as LAM). One hundred patients will be involved in this study (including control subjects) and ACME will again be used for performing a variety of statistical analyses.

No conclusions have been reached as yet concerning the best medication (methadone or LAM) since the study is still in the planning stages. The investigations as to the best dosage level and dosage schedules of methadone have given conclusive results, however. It has been shown that a dose of 50 mg per day is adequate for most patients, and that administering the entire dose once a day is best in terms of patient comfort.

There is a great mass of data involved in these studies, due to the number of questions being investigated and the large number of subjects about whom data is being collected. (The large number of subjects is necessary in a clinical trial of a drug to avoid having results biased by individual idiosyncrasies.) To record this mass of data by hand would require a great many man-hours; performing the complex and selective computations for the statistical analyses without the use of a computer would probably be impossible. In addition to its speed, ACME's interactive capability gives much-needed flexibility in the use and handling of data.

Since the methadone program is an ongoing treatment facility, using a drug and treating a disease about which there are still many unanswered questions, the need and opportunity for further study can be expected to continue for several years. Continued availability of the ACME facility will be vital to the success of such studies.

Investigator: Scott Grant
Dept. of Surgery, Div. of Ophthalmology
Project Began October 1971

Project: S_GRANT. CORNEA
Non-Realtime

The endothelial membrane of the cornea is being studied. This membrane is responsible for maintaining the proper hydration of the cornea via an active pumping process. One way of attacking the problem of understanding this pump is by the use of radioactive isotopes of Na and Cl. These tracers are used in perfusion studies of the endothelium. The amount of data gathered from each experiment is copious. The analysis of the results would require approximately six hours of uninterrupted manual calculation. Due to the delicacy and sensitivity of the mounted corneas, it has been necessary to repeat the experiments quite often to obtain statistically relevant results. The use of ACME in data analysis has allowed a job that once took six hours to be reduced to a fifteen to twenty minute period for data entry. More experiments can be carried out per week. Most important, the accuracy of the calculations is now unchallenged. This work has proceeded smoothly, providing further insight into this difficult problem.

Service Project Descriptions (cont'd.)

Further work has been initiated using ACME in the realm of mathematical modeling. One of the still unanswered questions about the cornea is why it is transparent. Electron micrographs are used to provide data on the ultrastructure of the cornea. This information is applied by the computer to evaluate the electromagnetic scattering of the cornea. An analysis of this sort is impossible without the assistance of ACME due to the several thousand data points of input.

Investigator: Paul Green
Dept. of Biosciences
Project Began September 1971

Project: P_GREEN. AVENA
Realtime

Biological Significance

The growth of plants is governed by a number of hormones each of which is a low-molecular-weight compound of known structure. These molecules are "keys" but the lock into which they fit is obscure. We treat the growing plant-object of choice, the oat (Avena) coleoptile, as a "black box" which we study by observing output (growth rate) as a function of step shifts in the driving force (turgor pressure). It can be shown that the growth process contains a governor or feedback system, with the feedback term coupled to the braking or deceleration component of the governor. The action of the hormone appears to involve a resetting of the coupling, giving less braking action, hence higher rate. A detailed characterization of the actual responses allows the description of a chemo-mechanical model for the growth process.

Computer Use

The analysis requires very accurate information of growth rate (accuracy of one part in 80,000, per minute). This is achieved by feeding voltage from a linear displacement transducer into a digital voltmeter (4 1/2 places). The information is then converted to paper tape using a teletype. As the experiments run for 12 hours, with a reading being taken every minute, this method keeps the information in the laboratory until the experiment is over and judged worthy of analysis. If so, the tape is read in, and length, rate, rate of change of rate, ln rate, etc. are computed. The change in various parameters allows us to characterize the action of ageing of the tissue, turgor pressure, and hormone action in abstract, but measurable terms.

Pertinence to Man

The system is a model for the study of the mechanisms for the cessation of growth (ageing). It also allows study of the action of a hormone of known chemical composition (indole acetic acid) on a biophysical system where the physical components (turgor pressure and wall parameters) are relatively well understood.

<u>Service Project Descriptions (cont'd.)</u>

Investigator: Samuel Kountz   Project: SLKOUNTZ. KIDNEY
Univ. of California Medical Center, San   Non-Realtime
  Francisco, Dept. of Surgery
Project Began December 1968

The Transplant Service at the University of California uses ACME in the
selection of recipients for renal homotransplantation. The computer has been
programmed to include data from over 100 patients who are on chronic hemo-
dialysis awaiting a cadaver transplant. When a cadaver kidney becomes avail-
able, similar data is obtained about the donor's body. The computer matches
donor information with recipient information. Matched recipients are then
brought into the hospital for transplantation.

ACME is also used as a follow-up tool to predict the onset of rejection crisis
by monitoring renal function and hemodynamic changes. Renal function is
measured by the single injection of radioisotopes. The disappearance curves
are analyzed by the computer and compared with previous determinations. This
has provided a very accurate method of following patients and detecting
early incipient rejection.

Using all of the available data on transplant patients, ACME generates survi-
val statistics. These are analyzed with the aim of finding factors signifi-
cant to rejection and survival.

Investigator: P. Herbert Leiderman   Project: PHLEIDER. PREMIE
Dept. of Psychiatry   Non-Realtime
Project Began December 1968

Studies of maternal behavior in non-human mammals have suggested that the de-
gree of interaction permitted between mother and infant in the postpartum
period will influence later maternal attachment and infant development. The
hypotheses raised by these studies can be explored with human mothers and
infants through manipulation of care procedures of mothers and newborns in
the immediate postpartum period.

Assessments of each mother and her infant are made periodically during the
time the infant is hospitalized and during the first two years at home.
Three major areas are included in these assessments:

  (1) maternal attitudes regarding her relationship with the child as
       reflected in responses to interviews and questionnaires;
  (2) maternal behavior observed during routine caretaking of the infant;
       and
  (3) the behavioral development of the infant.

A pilot study was conducted to determine the feasibility of changing premature
care procedures in order to study the effects of interactional deprivation in
the neonatal period on maternal attitudes and behavior. Forty-one mothers

Service Project Descriptions (cont'd.)

were permitted to enter the nursery and touch or handle their premature in-
fants in incubators as early as the second day after birth. The feasibility
of admitting mothers to the premature nursery without increasing the risk or
occurrence of infection, or disrupting the organization of the care of the
infants, was demonstrated.

We are now conducting a long-term study based on this pilot model to delin-
eate the differences in commitment, feelings of competence, and behavior in
the two differentially treated groups of mothers and to relate their behavior
to the motor and mental development of the infants.

Investigator: Harden McConnell   Project: H_MCCONN. ABSORB
Dept. of Chemistry   Realtime
Project Began February 1971

ACME is used for analysis of experimental paramagnetic resonance spectra and
calculation of theoretical spectra. These paramagnetic resonance spectra
arise from the application of the "spin label" technique to problems involv-
ing biological macromolecules. Biological problems which are currently being
studied include cooperative oxygen binding to the protein hemoglobin, the
relation of molecular orientation and motion to function in biological mem-
branes and membrane model systems, and development of quantitation assay
techniques using spin labels.

The paramagnetic resonance spectra that are obtained in spin label studies
are recorded as the first derivative of an absorption curve. The area under
the absorption curve is proportional to the number of spin labels giving rise
to the signal. Also, spin label spectra give information on changes in con-
formation or motion of a macromolecule. Frequently, these changes are de-
tected as a small change in the paramagnetic resonance spectrum. Quantita-
tive measurement of spectral changes requires normalization of spectra from
a series of experiments. ACME is used to compute the double integral of the
experimental spectrum and then to regenerate a normalized spectrum. Sub-
traction and addition of spectra are used to analyze experimental data. In
addition, experimental spectra are often analyzed by comparison with theo-
retical spectra which are calculated using ACME.

Interfacing Electronparamagnetic Resonance Spectrometers to the Computer

Models E-4 and E-12 of the Varian EPR Spectrometer have been interfaced to
ACME for purposes of real time data acquisition and data reduction. Analog
data from the spectrometer is sent to the 360/50 via a subsidiary computer,
the IBM 1800, at a rate determined by the user. A 16-bit analog-to-digital
converter converts the analog data to 10,000 digital values per scan for use
in the 360. Processed data is displayed on the spectrometers by the reverse
process.

The software for the system was designed for the following applications:

  (a) correction of spectra for baseline drift and systematic base-

Service Project Descriptions (cont'd.)

    line irregularities,

(b) calculation of relative concentrations of paramagnetic species in the sample (value of the double integral),

(c) normalization of different spectra to the same relative concentrations,

(d) simulation of complex spectra by appropriate addition of composite spectra,

(e) output of computer-calculated spectra to the EPR recorder for comparison with experimental spectra, and

(f) long term storage of and ready access to spectra.

Research Projects Involving Computing Capability

(1) Studies of the protein hemoglobin have led to a model which accounts for the binding of oxygen to normal human hemoglobin as well as the abnormal binding to mutant hemoglobins. Continued study of abnormal hemoglobins is in progress.

Many of the observations which led to the model resulted from accurate measurement of small deviations among experimental spectra. Both normalization of spectra and spectral addition have been used in this project. Many small programs have also been used to analyze data points (least squares, etc.).

(2) Investigation of the structure of biological membranes has led to characterization of a wide range of motions that contribute to the characteristic fluidity of such membranes. We are making quantitative measurements of the extent of fluid regions in membranes and of the rates of motion of membrane components. The studies are directed toward an understanding of such problems as virus attack on cell membranes, biosynthesis of membranes, and surface properties of transformed tumor cells.

ACME is used to normalize spectra so that differences between two states of a membrane may be determined. Also, many details of membrane motion have been deduced from theoretical analysis (performed on ACME) of the line shapes of the magnetic resonance spectra. For example, a set of reference spectra have been added, in proportions dictated by solutions to the diffusion equation, in order to simulate a series of experimental spectra which are dependent on the rate of lateral diffusion of membrane components. The observed rapid lateral diffusion of membrane components has important biological implications in such areas as membrane biogenesis and structural arrangement of membrane components.

(3) Electrochemical potentials are an essential feature of living cells. We are developing "molecular indicators" of both trans-membrane potentials and localized surface potentials in membranes. In these studies, we design spin labels so that their spectra depend on whether the label is outside or inside the membrane, or inside of the membrane-enclosed volume. In general, the spectra of the two species of spin labels are overlapping and must be separated for quantitative analysis. A general procedure is to use ACME to calculate the total integrated area of both spectra and then compare